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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/802,674	03/09/2001	Roberto A. Macina	DEX-0142	9969

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EXAMINER	
HARRIS, ALANA M	

ART UNIT	PAPER NUMBER
1642	11

DATE MAILED: 10/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/802,674	Applicant(s) MACINA ET AL.	
	Examiner Alana M. Harris, Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *6 and 8-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some *. c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4 & 8*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II (claims 1-5 and 7 wherein the GSG comprises SEQ ID NO: 3) in Paper No. 9, received August 6, 2002 is acknowledged. The traversal is on the ground(s) that the specification supports that both SEQ ID NO: 1 and SEQ ID NO: 3 are GSGs useful in the diagnosis of gastrointestinal cancer. This is not found persuasive because although the sequences may be related but require non-cohesive searches. As stated in Paper number 7, mailed May 6, 2002 they encode structurally and functionally distinct products.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-10 are pending.

Claims 6 and 8-10, drawn to non-elected inventions are withdrawn from examination.

Claims 1-5 and 7 are examined on the merits.

Information Disclosure Statement

3. The information disclosure statement filed July 16, 2001 as Paper number 4 cites references AD, AE, AQ, AR, AS and AU. However, those items were not in the application file, hence those references have been "penciled through" and have not been considered as to the merits. Applicants are invited to resubmit these items. Furthermore, Reference AD listed on page 4 of the IDS received July 16, 2001 cites

U.S. Patent number **6**,705,151. The Examiner has correctly identified the patent and listed it as U.S. Patent number **5**,705,151 (correction initialed by Examiner).

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-5 and 7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-5 and 7 are broadly drawn to methods of determining the level of GSG within cells, tissues or bodily fluids in a patient in order to diagnose, stage and monitor gastrointestinal cancer, wherein the GSG is polynucleotide sequence, SEQ ID NO: 3. The term "GSG" encompasses polynucleotides due to degeneracy in genetic coding, variations in nucleotide sequence, which allegedly encodes the same polypeptide as the native polynucleotide sequence. These diagnostic methods include for example *in situ* hybridization techniques, radioimunnoassays, as well as reverse transcription polymerase chain reaction.

The specification states that diagnostic markers utilized in the claimed invention are referred to as GSGs and more specifically Cln114 (galectin-4) and Cln115 (human carbonic anhydrase 1), see page 4, lines 5-8. Applicants have disclosed in the

specification several tables noting the relative levels of GSG expression in samples including cancerous samples versus matching normal adjacent samples, see Table 1, page 44; Table 2, page 45 and 46; Table 3, pages 47 and 48 and Table 4, pages 48-50. None of the data presented in the tables denotes the GSG as polynucleotide sequence, SEQ ID NO: 3. The obtained results set forth within the tables are not indicative of gastrointestinal cancer, but possibly tissue typing. Even if tissue typing was considered to be a valid utility the specification is not enabled. The specification does not enable one of ordinary skill in the art to definitively assess the incidence of any type of cancer, particularly gastrointestinal cancer in a patient. The evidence presented in the specification suggests that with the occurrence of Cln114 and Cln115 underexpression in colon cancer tissue this can be interpreted as diagnostic of gastrointestinal cancer, see bridging sentence of pages 46 and 47; page 50, lines 17-22. There is no nexus between the GSG identified as SEQ ID NO: 3 and GSGs, Cln114 and Cln115. This is not sufficient in implementing the GSG identified as SEQ ID NO: 3 in a molecular based diagnostic method for gastrointestinal cancer with the said sequence. Furthermore, Applicants have not provided any disclosure enabling the use of variant and degenerate polynucleotides of SEQ ID NO: 3. There is no disclosure designating what changes could be made within the polynucleotide sequence of SEQ ID NO: 3 and the consequent use of the resulting altered polynucleotides in the methods of diagnosing, staging and monitoring gastrointestinal cancer. The experimental design presented in the specification lacks information regarding the applicability of SEQ ID NO: 3 and its degenerate equivalent sequences in diagnostic methods relative to gastrointestinal

cancer. Furthermore as seen in the accompanying sequence datasheets the GSG identified as SEQ ID NO: 3 shares significant sequence homology with sequences from U.S. Patent 6,337,195 (issued January 8, 2002) and U.S. Patent 5,733,748 (IDS reference AA, Paper number 4, page 4). Those sequences are used in methods of diagnosing and colon cancer, which overlaps with Applicants' claimed invention of diagnosing gastrointestinal cancer in a patient. However, additional gastrointestinal sites include esophagus, pancreas and the stomach. It is not clear if Applicants' claimed methods are enabling for diagnosing cancers found within the aforementioned organs, which are included in gastrointestinal sites. It is not reasonable to conclude that SEQ ID: 3 and variants of this sequence would be effective in yielding a discriminate diagnosis between distinct disorders with distinguishing pathologies.

Applicants have not set forth any supporting evidence that suggests that SEQ ID NO: 3 is a unique tumor or molecular marker for gastrointestinal cancer. Tockman et al. (Cancer Research 52:2711s-2718s, 1992) teach considerations necessary for a suspected cancer biomarker (intermediate end point marker) to have efficacy and success in a clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other oncogenic disorders. Tockman teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials, see abstract. Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical

cancer and **if validated** (emphasis added) can be used for population screening (p. 2713s, column 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. "This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point [marker]", see page 2714s, column 1, Biomarker Validation against Acknowledged Disease End Points section. Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials, see page 2716s, column 2, Summary section. Tockman reiterates that the predictability of the art in regards to cancer prognosis and the estimation of life expectancies within a population with a disease or disorder are highly speculative and unpredictable.

Based on the analysis and the teachings presented above it would require undue experimentation for the skilled artisan to practice this invention because there is no support in the specification for the enablement of the broadly claimed invention. Therefore, in view of the insufficient guidance in the specification, extensive experimentation would be required to enable the claims and to practice the invention as claimed.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-5 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-5 and 7 are vague and indefinite in the recitation "GSG". This term is not well known in the art. Applicants should detail what the acronym stands for after the initial citing of the acronym. All claims thereafter can simply reference the acronym solely.

b. Claims 1-5 are vague and indefinite in the recitation "determining GSG levels". It is not clear what type of GSG molecules are to be measured. For purposes of examination the claims are interpreted as polynucleotide levels.

c. Claim 7 is indefinite in the recitations of non-elected subject matter. The claim references claim 6, as well as SEQ ID NO: 1, which are not examined.

Claim Rejections - 35 USC § 101

8. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. Claims 1-5 and 7 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial, credible or asserted utility or a well established utility.

Claims 1-5 and 7 are broadly drawn to methods of diagnosing the presence and metastases of gastrointestinal cancer in a patient, as well as methods of staging and monitoring gastrointestinal cancer comprising determining GSG (polynucleotide SEQ ID NO: 3) levels in cells, tissues or bodily fluid and comparing those levels with a normal human control. These methods include for example *in situ* hybridization techniques, radioimmunoassays, as well as reverse transcription polymerase chain reaction (RT-PCR), see page 22, line 15 –page 27, line 16. The specification states that diagnostic markers utilized in the claimed invention are referred to as GSGs and more specifically Cln114 (galectin-4) and Cln115 (human carbonic anhydrase 1), see page 4, lines 5-8. Applicants have disclosed in the specification several tables noting the relative levels of GSG expression in samples including cancerous samples versus matching normal adjacent samples, see Table 1, page 44; Table 2, page 45 and 46; Table 3, pages 47 and 48 and Table 4, pages 48-50. It is not clear from the tables what GSGs are indicative of SEQ ID NO: 3. Table 2 displays comparison between the cancerous and matching normal adjacent tissues such as from the cervix and kidney, as well as gastrointestinal sites. GSG expression is present in all of the different tissues with a high level of gastrointestinal tissue specificity. These results do not support Applicants' asserted use of the claimed methods for diagnosis, staging and monitoring of gastrointestinal cancer. There is no disclosure or working examples that demonstrate

the specifically asserted utility and evidences a substantial utility was well established at the time of filing. Applicants have provided information that simply supports the fact that GSGs, Cln114 and Cln115 are detectable in many tissue and possibly exclusively in gastrointestinal tissues. These GSGs have not been identified as any particular SEQ ID number. There is no information supporting the use of SEQ ID NO: 3 as a specific tumor marker to be implemented in the broadly claimed methods. The specification does not exemplify the use of the said sequences in differential expression in normal gastrointestinal tissue versus high risk (potentially diseased) gastrointestinal tissue/ gastrointestinal cancer tissue or their reliability as biomarkers, which may signal a stage of carcinogenesis. Based on the analysis set forth above the specification does not exemplify sufficient findings that constitute a specific, substantial or credible utility.

Claims 1-5 and 7 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by a specific, substantial or credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

10. Claims 1-5 and 7 are free of the art.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (703) 306-5880. The examiner can normally be reached on 6:30 am to 4:00 pm, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4315 for regular communications and (703) 308-4315 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)308-0196.

ALANA HARRIS
PATENT EXAMINER

Alana M. Harris, Ph.D.
October 17, 2002